REMARKS

Applicants respectfully request reconsideration of the application in view of the foregoing amendments and the following remarks.

Claims 1-4, 6-7, 10-11, 15, 17-18, 20, and 22 are amended herein to correct minor informalities.

Claim 30 has been cancelled and replaced with new claim 31. Support for this claim can be found, for example, in original claim 30. No new matter has been added by the amendments presented herein.

Claim Objections

Claims 1-4, 6, 7, 10, 17, 20, and 23 are objected to because, according to the Office Action, a comma should be inserted before the "wherein" phrases. In response thereto, Applicants have amended the above-referenced claims to insert a comma before the "wherein" phrases. Accordingly, Applicants assert that claims 1-4, 6, 7, 10, 17, 20, and 23, are in condition for allowance and respectfully request that the objection be removed and the claims allowed.

Claims 4 is objected to because, according to the Office Action, the word "which" should be replaced with "wherein the polynucleotide." In response thereto, Applicants have amended claim 4 as requested by the Examiner. Accordingly, Applicants assert that claim 4 is in condition for allowance and respectfully request that the objection be removed and the claim allowed.

Claims 7, 11, 15, and 18 are objected to because, according to the Office Action, "it is redundant to use both figure number and sequence identification number to identify the same sequence." In response thereto, Applicants have deleted the figure number from the objected-to claims. Accordingly, Applicants assert that claims 7, 11, 15, and 18 are in condition for allowance and respectfully request that the objection be removed and the claims allowed.

Claim 22 is objected to because, according to the Office Action, the word "wherein" should be inserted before "the expression cassette" in line 2. In response thereto, Applicants have amended claim 22 as requested by the Examiner. Applicants note that the addition of the word "wherein" necessitated changing the word "comprising" to "comprises" to maintain grammatical correctness. Accordingly, Applicants assert that claim 22 is in condition for allowance and respectfully request that the objection be removed and the claims allowed.

Claim 30 is objected to because, according to the Office Action, the word "comprising" in line 2 should be replaced with "wherein the method comprises". The Office Action further states that the phrase "whereby making a codon-optimized HPV 16 protein" should be added to the end of the claim. Applicants respectfully disagree with the objection, but nonetheless submit that the objection is moot. Claim 30 has been canceled herein without prejudice to the refiling of same in a related application. Applicants, therefore, respectfully request the reconsideration and withdrawal of the instant objection.

Rejections under 35 U.S.C. § 112, Paragraph Two

Claims 1 and 10 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Office Action states that the limitation "said polynucleotide sequence" in claim 1, line 3, lacks antecedent basis. In response thereto, Applicants have amended claim 1 to provide antecedent basis for the term "nucleotide sequence," which replaces the term "polynucleotide sequence" in the amended claim.

Further, the Office Action states that it is unclear what the term "which" refers to in claim 10, thus rendering the metes and bounds of the claim uncertain. In response thereto, Applicants have amended claim 10 to replace the term "which" with the phrase "wherein the polynucleotide encodes" so as to more particularly point out and distinctly claim the subject matter of the claimed invention.

Applicants assert that claims 1 and 10, as amended, are in condition for allowance and respectfully request that the rejection of these claims be removed and the claims allowed.

Rejections under 35 U.S.C. § 112, Paragraph One

Claim 30 is rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not enable any person skilled in the art to make and use the invention commensurate in scope with the cited claim. Specifically, the Office Action states that the specification is enabling for inducing an immune response to HPV16 infection using a polynucleotide encoding a codon-optimized HPV16 protein by intramuscular injection of the polynucleotide but does not provide enablement for inducing a protective immune response to HPV infection in a subject using a polynucleotide encoding a codon-optimized HPV16 protein by any route of administration. Applicants respectfully traverse.

Applicants respectfully disagree with the rejection, but nonetheless submit that the rejection is moot. Claim 30 has been canceled herein without prejudice to the refiling of

same in a related application. Applicants, therefore, respectfully request the reconsideration and withdrawal of the instant rejection.

Rejections under 35 U.S.C. § 103

Claims 1-4, 6, 10, 17, 21, 22, and 30 are rejected under 35 U.S.C. §103(a) as being unpatentable over the combined teachings of Zolotukhin et al. (U.S. Patent No. 5,874,304; hereinafter, "Zolotukhin"), Frazer et al. (U.S. Patent No. 6,489,141, hereinafter "Frazer") or WO 99/02694 (hereinafter "Frazer PCT") in view of Ludmerer et al., (U.S. Patent No. 5,952,216; hereinafter "Ludmerer") and Apt et al. (U.S. Patent No. 6,399,383, hereinafter "Apt"). The teachings of these references, in conjunction, are alleged to render the subject matter of claims 1-4, 6, 10, 17, 21, 22, and 30 obvious. Applicants respectfully traverse.

Specifically, the Office Action alleges that it would have been obvious to one of skill in the art at the time the invention was made to use the methods of Zolotukhin and Frazer "for efficiently producing HPV-16 proteins with a reasonable expectation of success." *See* Office Action, page 6, lines 7-10. The Office Action further alleges that "[t]he ordinary skilled artisan would have been motivated to modify the claimed invention because the improved efficiency of protein production." *Id.* at page 6, lines 10-11.

Applicants note that the initial burden of presenting a prima facie case of obviousness rests on the Examiner. *In re Oetiker*, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992). To establish a prima facie case of obviousness, the Examiner must show: (1) a suggestion or motivation in the prior art to modify or combine references; (2) a reasonable expectation of success and (3) that all of the claim limitations are taught or suggested by the prior art. MPEP § 2143. Only after a proper prima facie case of obviousness is established does the burden of rebutting the same shift to the Applicants.

In the present case, Applicants assert that the Examiner has failed to establish a prima facie case of obviousness because the prior art does not contain a suggestion or motivation to combine the cited references to arrive at the instant invention. Moreover, given the combination of references cited, one of skill in the art would not have had a reasonable expectation of success in selecting elements from each reference to piece together Applicants' invention.

(1) Motivation to Combine References

Federal Circuit law dictates that the mere possibility of combining references is insufficient to support a prima facie case of obviousness absent a specific suggestion in the prior

art as to the desirability of the combination. *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990). The Office Action concludes that the ordinary skilled artisan would have been motivated to "modify the claimed invention because the improved efficiency of protein production," (*see* Office Action at page 6, lines 10-11) but fails to cite any objective evidence or specific teaching of the prior art supporting the proposition that the prior art contained a motivation for one of ordinary skill in the art to combine the cited references at the time the application was filed.

To establish a prima facie case of obviousness, a motivation to combine references to arrive at the claimed invention must be found either explicitly or implicitly in the cited prior art. See MPEP § 2143.01. To establish an implicit showing of motivation to combine, it is important to consider the combined teachings of the cited references, as well as the nature of the problem to be solved as a whole. Applicants respectfully submit that the Office Action fails to disclose any language in the prior art whatsoever that would suggest the desirability of combining the elements that comprise Applicants' invention. None of the cited references by Zolotukhin, Frazer, Ludmerer or Apt presents an explicit motivation to combine the references to codon-optimize HPV-16 genes for high level expression in human cells. Moreover, Applicants respectfully submit that none of the cited references contain an implicit motivation to combine because none of the cited references disclose the existence of a problem expressing high levels of HPV-16 early and late genes in human cells.

Zolotukhin was cited for teaching humanized versions of jellyfish green fluorescent protein (GFP) genes for high level expression in mammalian cells, expression constructs, methods of using such, and adenoviral vector comprising the humanized GFP sequences. The need to "humanize" jellyfish GFP in Zolotukhin arose from the inventors' inability to express this gene, which is from an organism that is evolutionarily far removed from humans, in a human cell for use as a reporter gene. Zolotukhin does not address or suggest use of "humanization" for HPV genes. In fact, there is nothing in Zolotukhin at all that would suggest "humanization" of viral genes for use in gene therapy. Additionally, there is no discussion in Zolotukhin related to the desirability of increasing the expression of viral genes, or the inability to express sufficient quantities of any viral antigens. Applicants respectfully submit that the disclosure of Zolotukhin is lacking in any information that would lead one of skill in the art to apply their method of "humanization" to HPV-16 genes.

Frazer and Frazer PCT were cited for teaching "a method of constructing a synthetic polynucleotide from which a protein is selectively expressible in a desired cell, wherein at least one codon is replaced with a synonymous codon to produce a synthetic polynucleotide having altered translational kinetics." Office Action at page 5, first full paragraph. The office

action further states that Frazer teaches that "papillomaviral late proteins such as L1 protein is very difficult to produce at a sufficient level." *Id.*

Frazer does not disclose codon-optimization of HPV-16 early and late genes, but rather limits its discussion of papillomavirus codon-optimization to bovine papillomavirus type 1. Applicants respectfully submit that there is no motivation in the Frazer reference to codon-optimize HPV-16 genes because their disclosure is limited to BPV-1. Frazer in no way discusses the need to codon-optimize HPV-16 early and late genes for expression in human cells. Applicants note that, though both in the same family, HPV-16 is not the same virus as BPV-1. It follows that discussion of BPV-1 is not necessarily applicable to HPV-16, particularly given that the two viruses cause different diseases. More specifically, BPV-1 causes cutaneous fibropapillomas (plantar's warts), similar to HPV-1, wherein HPV16 causes infections of the genital mucosa.

Applicants respectfully disagree with the statement that the Frazer background section teaches "papillomaviral late proteins such as L1 protein is very difficult to produce at a sufficient level." A complete reading of the background section of Frazer shows that Frazer focuses on the problem of selective delivery of genes to specific target tissues, and, more particularly, to the inability to express PV late genes in non-differentiated cells. More specific discussion and examples are presented within the Frazer specification that show synthetic versions of GFP, BPV1 L1 and BPV1 L2. Frazer fails to disclose the need to produce increased expression *of HPV-16* in human cells, or other information relevant to HPV16. The Office Action fails to identify any statement of the Frazer reference that teaches that there are constraints on expression of HPV-16 early and late proteins in human cells. In fact, Frazer fails to discuss PV early genes at all. Frazer, therefore, does not disclose any motivation to combine their study with that of Zolotukhin, Ludmerer, and Apt to arrive at the presently claimed invention.

Ludmerer et al. also fails to disclose a motivation to combine the cited references or to teach or suggest the present invention. Ludmerer is cited for teaching that "HPV-16 is responsible for epithelial dysplasia and are associated with many types of invasive carcinomas, and the desirability to produce HPV-16 specific proteins including E1-E7, L1 and L2 for research and diagnosis." Office Action at page 5, lines 16-19. Applicants respectfully submit that, contrary to the assertion in the Office Action, Ludmerer does not teach "the desirability to produce HPV-16 specific proteins including E1-E7, L1, and L2." Ludmerer teaches HPV16 neutralizing epitopes and synthetic HPV-16 virus-like particles comprising HPV16 L1 proteins with specific mutations, said VLPs being useful in distinguishing and characterizing immunological responses to HPV16 infection or vaccination. Ludmerer further teaches the use

of said synthetic VLPs in assays designed to monitor serological responses to HPV16 infection. Ludmerer does not disclose or suggest codon-optimization or HPV-16 genes because the goal of Ludmerer was to change the immunological character of HPV16 L1, not to increase the amount of gene expression.

As stated above, MPEP § 2143.01 dictates that the motivation to combine references must be found either explicitly or implicitly in the cited prior art to establish prima facie obviousness. In the present case, the Office Action fails to allege any explicit teaching in Ludmerer that suggests the desirability of codon-optimizing HPV-16 genes for high level expression in human cells. The Office Action also fails to identify any statement of the Ludmerer reference which teaches that there are constraints on expression of HPV-16 early and late proteins in human cells. Because Ludmerer does not even teach that such a problem expressing HPV genes in human cells even existed, the skilled artisan would not have been motivated to combine elements of the cited references to arrive at the present invention based upon the Ludmerer disclosure.

The deficiencies of the cited art by Zolotukhin, Frazer, and Ludmerer are not remedied by the disclosure of Apt, which also fails to provide a motivation to combine references. Apt is cited for allegedly teaching that "HPV 16 is highly oncogenic, and using various HPV proteins for developing vaccines." *See* Office Action at page 5, lines 19-20. Applicants respectfully disagree with this statement and dispute the relevance of the Apt disclosure to the instant application. In fact, Applicants submit that the Apt disclosure teaches away from the instant invention for reasons that follow.

Apt teaches the use of *low-risk* HPV types, particularly HPV-2, HPV-27 and HPV-57, *as vectors* for gene delivery, such vectors being "particularly useful for expressing foreign proteins in the skin of human patients." *See* Apt at column 6, lines 58-59. Because the goal of the Apt disclosure is to introduce foreign genes into human tissue using HPV *as vectors*, preferred HPV types are those which lack oncogenic potential and direct foreign gene expression to cutaneous tissue. Apt does not disclose or suggest the use of HPV genes *as antigens* for the prevention and/or treatment of HPV infection and associated HPV disease. One of skill in the art, following the disclosure of Apt, would not be motivated to choose HPV16 for vaccine purposes because Apt teaches that for use as vectors for gene therapy, one should utilize the E1 and E2 coding sequences from benign or low-risk HPVs and specifically suggests using HPV-1, -2, -3, -4, -6, -7, -10, -11, -27, -28, -29, -48, -50, -57, -60, ,63, and -65 (*see* Apt, column 8, lines 2-5). In addition, Apt teaches that disorders amenable to treatment with the HPV gene therapy vectors described therein include genetic diseases such as cystic fibrosis, sickle cell anemia, b-thalassemia, phenylketonuria, galactosemia, and Wilson's disease (see Apt, column 10 "Genes

for Expression in Gene Therapy"). Apt further teaches that HPV gene delivery vehicles can be used to treat autoimmune conditions, inflammation, allergy, asthma, obesity and to express immunogenic epitopes of pathogenic microorganisms such as clostridia, molluscum contagium, herpes, meningococci, fungi, pseudomonas, staphylococci, and streptococci. *Id.*

Apt does not suggest the use of polynucleotides encoding HPV proteins from oncogenic HPV types as immunogens for the purpose of inducing an immune response against HPV. Apt does not disclose codon-optimization or any other means for increasing gene expression. Additionally, Apt fails to disclose the desirability of increasing expression of HPV16 early and late genes in human cells. In stark contrast, the present invention discloses the use of codon-optimized HPV genes as antigens to induce an immune response against HPV. In that respect, a preferred HPV type of the present invention is HPV16 because of its oncogenic potential. While the disclosure of Apt teaches the skilled artisan to avoid oncogenic HPV types, the present invention teaches that "[i]t is preferred that the HPV chosen be one which is known to cause a pathological condition in humans." *See* Specification at page 7, lines 2-3. For this reason, the present application specifically suggests the use of HPV types 6a, 6b, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 68. *Id.* at lines 6-9.

In attempting to establish a case for "motivation to combine" the Office Action merely summarizes the teachings of the cited references and couples said summaries with broad conclusory statements that one of skill in the art would have had a motivation to combine said references. Without a specific motivation to combine prior art references, Applicants submit that the rejection of claims 1-4, 6, 10, 17, 21, 22 and 30 as obvious over the cited prior art is improperly based on hindsight knowledge using the present specification as a blueprint. The Federal Circuit has repeatedly cautioned against employing hindsight to reconstruct the claimed invention out of isolated teachings from the prior art. *See, e.g., Grain Processing Corp. v American Maize-Products Co.*, 5 U.S.P.Q. 2d 1788 (Fed Cir. 1988). Accordingly, the prohibition against "hindsight reconstruction" counsels against a finding of obviousness of the claimed subject matter in the present case.

(2) Reasonable Expectation of Success

Applicants further submit that the Office Action fails to present a proper prima facie case of obviousness because, given the cited combination of references, one of ordinary skill in the art would not have had a reasonable expectation of success in developing the claimed invention.

Applicants submit that codon-optimization is not always successful at increasing expression of a particular gene. In that regard, the Examiner's attention is drawn to the declaration of Applicant William L. Mcclements, who states that his experience with codon-optimization, prior to filing the instant application, led to unsuccessful attempts at increasing the expression of the gD and gB genes from Herpes simplex virus type 2 (HSV2). He also notes that successful codon-optimization of one gene is not predictive of the future success of a different gene. As stated above, though BPV-1 and HPV16 are from the same family, one of skill in the art would not expect them to behave similarly because they are different viruses and cause different diseases.

Moreover, the Mcclements declaration summarizes art that was available to the skilled artisan at the time the instant application was filed, that identify inhibitory sequences and mRNA instability elements present in the HPV16 L1 and L2 genes, which could account for low expression levels of the HPV16 late genes. While the Frazer reference states that an attempt was made to eliminate putative inhibitory sequences from BPV L1, which resulted in expression of BPV1 L1 mRNA but not protein, their study did not include HPV-16. Applicants therefore submit that the state of the art at the time the present application was filed demonstrates that there was not an expectation of success at codon-optimizing HPV16 genes for high-level expression in human cells.

Applicants therefore assert that Claims 1-4, 6, 10, 17, 21, 22 and 30 are not obvious over the prior art teachings of Zolotukhin in combination with Frazer in view of the teachings of Ludmerer and Apt, as discussed above. Accordingly, Applicants respectfully request that the rejection of these claims based upon 35 U.S.C. § 103 be removed and the claims allowed.

Claims 19, 20 and 23 are rejected under 35 U.S.C. §103(a) as being unpatentable over the combined teachings of Zolotukhin and Frazer in view of Ludmerer and Apt, as discussed above, and further in view of Ertl et al. (U.S. Patent No. 6,019,978, herinafter "Ertl") and Donnely et al. (*J. Infect. Diseases* 713: 314-20 (1996); hereinafter "Donnelly"). The teachings of these references, in conjunction, are alleged to render the subject matter of claims 19, 20, and 23 obvious. Applicants respectfully traverse.

Claims 19, 20, and 23 are generally drawn to adenoviral vaccine vectors comprising a polynucleotide encoding a codon-optimized HPV16 protein and a vaccine plasmid comprising a polynucleotide encoding a codon-optimized HPV16 protein. Applicants herein reiterate arguments presented above related to the cited references by Zolotukhin, Frazer, Ludmerer, and Apt. Applicants submit that claims 19, 20, and 23 are not obvious in light of the

cited art because the deficiencies of Zolotukhin, Frazer, Ludmerer, and Apt are not remedied by Ertl or Donnelly.

Ertl was cited for allegedly teaching an adenoviral vector comprising complete or partial deletions in E1 and E3, the vector comprising a portion of a plasmid and a portion of adenovirus genome, a CMV promoter operably linked to the polynucleotide, wherein the encoded sequences in the E1 deletion site could be HPV L1, E6, and E7, wherein the vector could be used to induce a protective immune response against HPV via single or multiple dosing regimen. Ertl does not teach codon-optimization or methods of increasing gene expression. Ertl does not teach the need or desire for increased gene expression of HPV16 genes, nor does it contain any disclosure specific to HPV16.

The Office Action fails to allege any explicit teaching in Ertl that suggests the desirability of codon-optimizing HPV-16 genes for high level expression in human cells. The Office Action also fails to identify any statement of the Ertl reference which teaches that there are constraints on expression of HPV-16 early and late proteins in human cells. Because Ertl does not even teach that such a problem expressing HPV genes in human cells even existed, the skilled artisan would not have been motivated to combine elements of the cited references to arrive at the present invention based upon the Ertl disclosure. Therefore, Ertl does not remedy the stated deficiencies of Zolotukhin and Frazer in view of Ludmerer and Apt.

Donnelly also fails to provide the motivation to combine references that is absent from Zolotukhin, Frazer, Ludmerer, Apt, and Ertl. Donnelly was cited for allegedly teaching a polynucleotide encoding a cottontail rabbit papillomavirus HPV11 L1 and L2 protein in an expression vector V1J derivative V1Jns. As above, Donnelly fails to disclose codon-optimization or methods of increasing gene expression. Donnelly does not teach the need or desire for increased gene expression of HPV16 genes, nor does it contain any disclosure specific to HPV16. Applicants note that the Donnelly disclosure is limited to vectors comprising a polynucleotide encoding a cottontail rabbit papillomavirus (CRPV) protein and not HPV-11, contrary to the assertion of the Office Action. The Office Action fails to allege any teaching of Donnelly that suggests the desire to combine the cited references to arrive at the presently claimed invention.

Applicants therefore assert that Claims 19, 20, and 23 are not obvious over the prior art teachings of Zolotukhin in combination with Frazer in view of the teachings of Ludmerer, Apt, Ertl, and Donnelly, as discussed above. Accordingly, Applicants respectfully request that the rejection of these claims based upon 35 U.S.C. § 103 be removed and the claims allowed.

Summary

Applicants respectfully submit that all outstanding rejections have been overcome by the amendments herein and remarks above. Accordingly, Applicants maintain all claims are in condition for allowance and a favorable action on the merits is earnestly solicited.

If the Examiner believes that a telephone conference would be of value, she is requested to call the undersigned counsel at the number listed below.

Respectfully submitted,

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